REMARKS

Preliminary Remarks

Claims 1 and 3-24 are pending in this application. On page 2 of the advisory action, the examiner suggested that applicants file the receipt stamped by the OIPE, dated October 25, 2001, in order to clear the record regarding the date of the response filed to Paper No. 9. The applicants, pursuant to this request by the examiner, enclose a copy of the response filed on October 25, 2001 with a receipt stamped by OIPE, dated October 25, 2001.

In view of the foregoing, the applicants request that the examiner acknowledge this error. The applicants also request that the Patent Office acknowledge this delay in examination in view of the term of any patent issuing from the present application.

Patentability Remarks

Rejection under 35 U.S.C. §103(a)

The examiner has maintained the rejection of claims 1 and 3-24 under 35 U.S.C. §103(a) as allegedly being unpatentable over Engel *et al.* (European Patent Application Number 97100852.9)(hereafter Engel), Albano *et al.* (Human Reproduction, 11:2114-2118 (1996))(hereafter Albano), Felberbaum *et al.* (10th World Congress On In Vitro Fertilization and Assisted Reproduction, Vancouver, Canada, May (1997))(hereafter Felberbaum), and Garfield (U.S. Patent Number 5,470,847)(hereafter Garfield), in view of Deghenghi (U.S. Patent Number 5,945,128)(hereafter Deghenghi), Rabasseda *et al.* (Drugs of the Future 24:393-403 (1999))(hereafter Rabasseda), and Kent (U.S. Patent Number 4,016,259 (1977))(hereafter Kent).

The examiner maintains the citation of seven different and unrelated documents to find the presently claimed invention obvious. Specifically, the examiner alleges the LHRH-

antagonists such as cetrorelix, teverelix, antide, and ganirelix are know to be LHRH-antagonists and known to be useful in the methods of controlled ovarian stimulation and assisted reproductive technique and of the treatment of infertility according to Engel, Albano, Felberbaum, Deghenghi, and Rabasseda. Thus, the examiner further alleges that each step in the instant claimed methods is known in the prior art. The examiner then asserts that the particular estrogen used (mestranol) in oral contraceptive preparations in combination with progestogen are well known contraceptive agents and are broadly known to be useful in the therapeutic management of infertility according to the prior art. Therefore, the examiner alleges that one of ordinary skill in the art would have reasonably expected that combining these particular agents would produce additive therapeutic effects to improve the treatment of therapeutic management of infertility, absent evidence to the contrary. In addition, the examiner concludes that the applicants' results provide no clear and convincing evidence of nonobviousness or unexpected results over the cited prior art since there is no side by side comparison with the closest prior art and that motivation to combine the teachings of the prior art to make the present invention exist.

The applicants respectfully traverse the foregoing rejection and request reconsideration and withdrawal of the rejection. Further to the examiner's comments with respect to a side-by-side comparison of the cited documents and the claimed invention, the applicants present their response in a manner to answer the examiner's concerns and ultimately in order to demonstrate that the cited documents do not render the present invention obvious.

To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to

combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, not in the applicant's disclosure. *In re Vaeck*, 947 F.2d 488 (Fed. Cir. 1991).

The examiner bears the burden of establishing a prima facie case of obviousness and "can satisfy this burden only by showing some objective teaching in the prior art or that knowledge generally available to one of ordinary skill in the art would lead that individual to combine the relevant teachings of the references." *In re Fine*, 5 U.S.P.Q.2d 1598 (Fed. Cir. 1988). To support a conclusion that a claimed composition is obvious, either: (a) the references must expressly or impliedly suggest the claimed composition to one of ordinary skill in the art, or (b) the examiner must present a convincing line of reasoning as to why a person of ordinary skill in the art would have found the claimed invention to have been obvious in light of the teachings of the references. *Ex parte Clapp*, 227 U.S.P.Q. 972, 973 (Bd. Pat. App. & Inter. 1985).

The applicants submit that Engel, Albano, Felberbaum, and Garfield, either alone or in combination with Deghenghi, Rabasseda, and Kent neither teach or suggest the applicants' claimed invention, *i.e.*, a method of therapeutic management of infertility by programming of controlled ovarian stimulation and assisted reproductive procedures the improvement consisting of (a) suppression of premature ovulation with an LHRH-antagonist in controlled ovarian stimulation and assisted reproductive techniques with multiple follicle and oocyte development; (b) programming the start of controlled ovarian stimulation by the administration to a patient of progestogen only –preparations or, alternatively, combined oral contraceptive preparations; (c) exogenous stimulation of the ovarian follicle growth; (d)

ovulation induction with HCG, native LHRH, LHRH-agonists or recombinant LH; and (e) application of assisted reproduction techniques, especially of IVF (in-vitro-fertilization), ICSI (intracytoplasmic sperm injection), GIFT (gamete intra-Fallopian transfer), ZIFT (zygote intra-Fallopian transfer) or by intrauterine insemination by sperm injection, wherein onset of patient's menstrual cycle and of controlled ovarian stimulation are programmed in order to perform oocyte pickup and fertilization procedures during Mondays to Fridays.

With respect to Engel, the first primary document, the examiner specifically alleges Engel teaches a method of using an LHRH-antagonist for suppressing premature ovulation and assisted reproductive techniques. With regard to Engel, there is no teaching or suggestion for administrating progestogen-only containing preparations and/or oral contraceptives for programming of COS/ART (controlled ovarian stimulation/assisted reproductive technologies). These medications are used to manipulate the menstrual cycle at any point during the cycle by resetting and beginning a new menstrual cycle. This is accomplished by administering oral contraceptives or progestogen-only containing preparations over a few days and are then withdrawn. As a result, all hormones related to the menstrual cycle (LH, FSH, progesterone etc.) decrease. As a consequence, the corpus luteum degenerates, menstrual bleeding occurs, and a new menstrual cycle is initiated. By using these medications to set and start a new menstrual cycle, an optimal schedule for coordinating the application of COS/ART (controlled ovarian stimulation/assisted reproductive technologies) procedures can be achieved (see specification at page 3, line 24 to page 4, line 4). Thus, oral contraceptives or progestogen-only containing preparations are used for programming the application of COS/ART procedures. Engel does not teach the administration of oral contraceptives or progestogen-only containing preparations for resetting the menstrual clock as directed by the applicants' claims (claim 1). Rather than teaching or at a minimum suggesting the applicants' claimed invention, Engel merely teaches

carrying out controlled ovarian stimulation (COS) using LHRH agonist and antagonist. Engel's protocols fail to coordinate the exact start date of a menstrual cycle by the administration of progestogen-only containing medications and/or oral contraceptives. The applicants' teachings demonstrate a specific timing of oral contraceptives or progestogen-only containing medications must occur. The co-administration of medications with gonadotropins and LHRH analogues (LHRH agonists or LHRH antagonists) would have deleterious effects on the growth and development of follicles, and thus oocyte maturation, due to complex hormone feed-back mechanisms and direct effects on the follicles and endometrium. In fact, Engel teaches away from administering progestogen-only containing medications and/or oral contraceptives at any point in their disclosed protocol, because the goal of Engel's teachings is to lower the level of progesterone as low as possible in the follicular phase so LHRH antagonist can prevent the premature LH surge/ovaluation. Thus, one of skill in the art, studying the disclosure of Engel in view of the contradictions (progestogen-only containing medications and/or oral contraceptives administration vs. LHRH antagonist or gonadotropin administration) would have no suggestion of resetting the menstrual cycle using progestogen-only containing medications and/or oral contraceptives medications in order to coordinate exact application of COS/ART procedures.

With regard to Albano *et al.*, the second primary reference, the examiner cites this reference for its alleged teaching of a method of using cetrorelix in suppression of premature ovulation in controlled ovarian stimulation and assisted reproductive techniques, such as in-vitro fertilization or intracytoplasmic sperm injection, and that progesterone concentration is significantly lowered due to administration of cetrorelix. The applicants submit that Albano *et al.* do not provide any teaching or suggestion of programming the start of controlled ovarian stimulation by the administration to a patient of progestogen only-preparations and/or combined oral contraceptives preparations (claim 1). In fact, the applicants submit that

Albano *et al.* teaches away from administering progestogen-only preparations alone or in combination with oral contraceptives for the purpose of elevating progesterone levels because Albano *et al.* reports the use of cetrorelix (LHRH-antagonist) to not only decrease progesterone levels significantly, but prevent premature LH surges and ovulation. After the menstrual cycle is reset and has begun, the applicants also teach lowering the levels of progesterone through administration of gonadotropins and cetrorelix (on day 8) to not only stimulate the ovaries and induce oocyte growth, but also to prevent premature LH surge. However, the applicants teach that the use and then subsequent withdrawal of progestogen-only preparations is a necessary step in starting a new menstrual cycle in order to optimize the timing for applying COS/ART procedures. Accordingly, applicants respectfully submit that one of skill in the art would not find any suggestion of the use of progestogen-only preparations alone or in combination with oral contraceptives to coordinate and optimize conditions for COS/ART procedures in light of Albano *et al.*

The examiner cited Felberbaum *et al.*(the third primary reference) for its alleged teaching of the usefulness of LHRH-antagonists in a method of suppressing premature ovulation in controlled ovarian and assisted reproductive techniques. The examiner also alleged that Felberbaum *et al.* taught a profound suppression of LH and a less pronounced suppression of FSH. The applicants submit that inhibition of LH or FSH occurs as a consequence of LHRH antagonist administration. However, Felberbaum *et al.* does not report the administration of progestogens nor oral contraceptives to restart the menstrual cycle in order to properly coordinate the COS/ART procedures, i.e., the controlled ovarian stimulation protocol. Accordingly, as discussed above, the applicants respectfully submit that one of skill in the art would not find any suggestion of the use of progestogens-only preparations alone or in combination with oral contraceptives to coordinate and optimize conditions for COS/ART procedures in light of Felberbaum *et al.*

With regard to Garfield, the fourth primary document, the examiner alleged this disclosure teaches a method of using progestogen, together with an estrogen and an LHRH-antagonist, during the follicular phase of the menstrual cycle for controlling ovarian stimulation and preventing conception. Garfield's teachings are in direct contrast to the goals of applicants' claimed invention. As discussed above, deleterious effects on the follicles occurs if progestin (and in combination with estrogen) is administered during the follicular phase of the menstrual cycle in combination with LHRH antagonist. These drugs cause high levels of progesterone and estrogen levels to be produced, which not only inhibit LHRH and the LH surge, but also prevent ovulation. Once COS/ART cycling procedures have begun, high levels of progesterone during the follicular phase are unwanted. Garfield's methods are to prevent ovulation, and thus conception via implantation of an embryo in a non-stimulated menstrual cycle, which is in direct contrast to the goals of applicants' claimed method. In addition, applicants' invention teaches using progestin and an estrogen/estradiol combination thereof to only control the beginning of a menstrual cycle and thus coordinate the time of a COS/ART protocol in order to maximize the chance for extra-corporal fertilization and embryo transfer in a woman. Accordingly, applicants respectfully submit one of skill in the art would not find using programmed ovarian stimulation protocol to coordinate the timing of the start of the menstrual cycle with COS in order to undertake oocyte pick-up, fertilization procedures and embryo transfer from Mondays to Fridays when qualified staff and equipment are at hand (claim 1) in light of Garfield.

The examiner cited Deghenghi for its alleged teaching of the LHRH-antagonists cetrorelix, teverelix, ganirelix and antide. The applicants submit that this first secondary document does little to overcome the failings of all primary documents. Specifically, Deghenghi does not teach or suggest the administration of LHRH antagonists for short term use during the menstrual cycle in order to prevent LH surge and thus premature ovulation.

Rather, Deghenghi teaches long term administration of LHRH-antagonists cetrorelix, teverelix, ganirelix, and antide in men to decrease the levels of testosterone and LH to values found in castrated males. Furthermore, Deghenghi teaches away from the goal of using COS/ART procedures to obtain viable pregnancies by teaching that long term administration of LHRH antagonists actually impairs the implantation of the embryo and results in loss of pregnancy. Finally, Deghenghi does not teach or suggest the administration of progestogens, or in combination with contraceptive pills comprising estradiol and progestogens to manipulate the start of the menstrual cycle in order optimize the timing of COS/ART procedures. The applicants teach a controlled administration of different hormones to not only control COS/ART procedures, but also a short term application of LHRH antagonists to temporarily suppress LH levels/premature ovulation to allow for release of mature oocytes upon administration of human chorionic gonadotropin (HCG) (see page 4, lines 13-18). Accordingly, the applicants submit that one of skill in the art would not find any suggestion of using LHRH antagonist for short term use to prevent premature LH surge/ovulation in a COS/ART cycle nor using progestogens at the end of the luteal phase, and thereafter withdrawing the progestogens in order to start a new menstrual cycle for optimizing application of COS/ART procedures in light of Deghenghi.

The examiner alleged that Rabasseda *et al.* is cited for its' alleged teaching that LHRH antagonists such as cetrorelix, ganirelix, and abarelix are known in the treatment of female infertility. The applicants submit that Rabasseda *et al.* does little to overcome the failings of all primary documents and Deghenghi. Specifically, although Rabasseda *et al.* states that ganirelix is designed as an LHRH antagonist to be used with FSH for controlled ovarian stimulation before IVF or intracytoplasmic sperm injection, the use of ganirelix also prevents premature LH surges. The applicants further submit that Rabasseda *et al.* declared a decrease not only in LH, but also estradiol levels following injection of ganirelix in

COS/ART protocols. In contrast, these results following injection of other LHRH antagonist in woman undergoing COS have not been observed by the applicants. Moreover, Rabasseda *et al.* fails to teach or suggest the use of progestogens or combination of progestogens with estradiol (oral contraceptives) for the manipulation of the start of a new menstrual cycle in order to coordinate and carry out COS and ART procedures at predestined days and times within the menstrual cycle of a woman when qualified staff and equipment is on hand. Accordingly, the applicants respectfully submit one of skill in the art would not find using ganirelix to prevent LH surges would manipulate the exact timing for carrying out the COS and ART procedures at predestined days and times within the menstrual cycle of a woman (claim 1).

Finally, the examiner alleges that Kent discloses that the combination of progestogens and estrogen is useful in animal contraception. The applicants submit that Kent does little to overcome the failings of all primary documents in view of Deghenghi and Rabasseda *et al.* Although Kent teaches that contraceptives for animals, including humans, are steroidal in nature and the use of progestogens such as norethindrone and ethynodiol with estrogens such as ethynyl estradiol and mestranol are used, the use of progestogens or combinations of progestogens with estradiol in programming COS/ART by manipulating the start of the menstrual cycle is not taught. In addition, Kent does not teach using LHRH antagonists, *i.e.* cetrorelix, for preventing premature LH surges and thus ovulation in COS/ART cycles. Thus, there is nothing in the cited document that would lead a skilled artisan to conclude that use of progestogens with estradiol can be used to control the beginning of the menstrual cycle and using LHRH antagonist for controlled ovarian stimulation are both used to program the time of the COS/ART cycle in order to perform oocyte pickup and fertilization procedures during Mondays to Fridays (claim 1).

In summary, applicants submit that Engel *et al.*, Albano *et al.*, Felberbaum *et al.*, and Garfield, in view of Deghenghi, Rabasseda *et al.*, and Kent, either alone or in combination, neither teach nor suggest the applicants' claimed invention. Accordingly, without such teaching or suggestion, the examiner has not established a *prima facie* case of obviousness. Therefore, withdrawal of the rejections based upon 35 U.S.C. §103(a) is respectfully requested.

III. CONCLUSION

In view of the foregoing, the claims are still believed to be in form for allowance, and such action is hereby solicited. If any point remains in issue which the examiner feels may be best resolved through a personal or telephone interview, the examiner is **strongly urged** to contact the undersigned at the telephone number listed below.

Respectfully submitted,

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